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EXAMINER
HA, JULIE

ART UNIT	PAPER NUMBER
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,948	EHRENPREIS, ELI D.	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *13-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Election/Restriction filed on February 07, 2007 is acknowledged. Claims 1-40 are pending in this application.

Restriction

1. Applicant's election with traverse of Group I (claims 1-12) drawn to a method of monitoring gastric emptying and the election of species of D-xylose in the reply filed on February 07, 2007 is acknowledged. The traversal is on the ground(s) that the present invention stems from the discovery that use of "commercially available, nonradiographic substances" that are amenable to being detected using a simple blood test. Measurements of serum levels of the agents are used to estimate gastric emptying and to diagnose delayed gastric emptying. Thus, both the claims of Group I and the claims of Group II involve the step of determining the amount of time taken for an elevated concentration of the detection agent to be found in the blood stream. Thus, a search designed to identify art relevant to the claims of Group I will likely be substantially co-extensive with the search designed to identify art relevant to the claims of Group II. Moreover, the claims of Group III are merely directed to exemplary kits for use in performing the methods of Groups I and II. This is not found persuasive because the inventions restricted are patentably distinct. The search for each of the inventions is not co-extensive particularly with regard to the literature search. Burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for foreign references and literature searches. Burden also resides in the

examination of independent claim sets for clarity, enablement, and double patenting issues. Further, a reference that would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Finally, the consideration for patentability is different in each case. Thus, it would be an undue burden to examine all of the above inventions in one application and the restriction for examination purposes as indicated above is deemed proper.

The requirement is still deemed proper and is therefore made FINAL.

Claims 13-40 are withdrawn from consideration as being drawn to a nonelected Invention. During the course of search for D-xylose, acetaminophen was found pertaining to agent being used for evaluation of gastric emptying. Therefore, search was extended to include claim 6. Claims 1-12 are examined on the merits in this application.

Objection-Minor Informality

2. The title is objected to because of the following informalities: The title is too long. The title is limited to 5-7 words maximum.

Appropriate correction is required.

Rejection-35 U.S.C. § 112, 2nd

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 1 recites the limitation "the blood" in claim 1b. There is insufficient antecedent basis for this limitation in the claim.

6. Claim 2 recites “elevated concentrations to be found in the blood of said mammal is greater than five minutes”. The words “greater than five minutes” is unclear since this can mean any time point from 5 minutes 1 second to infinity.

Rejection-35 U.S.C. § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3, 7-8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Gamst ON (Scandinavian Journal of Gastroenterology, 1989; 44(163): 44-47).

9. The instant claims are drawn to a method of monitoring gastric emptying in a mammal comprising a) administering a formulation comprising an agent that is formulated in a delayed-release formulation that prevents said agent from being released into the gastrointestinal tract when the pH of the gastrointestinal tract is lower than about 6.0, and b) determining the amount of time taken for an elevated concentration of said agent to be found in the blood of said mammal is greater than five

minutes, and the agent is not present in normal dietary substances. Additionally, the claims are drawn to an agent that is encapsulated in a pH-sensitive formulation and the agent is non-isotopic. Claims are further drawn to said agent is not elevated in the blood stream 120 minutes post-administration.

10. Gamst ON teaches that the absorption of naproxen is dependent on the gastric emptying and the dissolution of the drug product in the small intestine. Enteric-coated granules designed to dissolve at pH 5.5 have delayed absorption profile when given orally. By varying the coating layer, it is possible to monitor the dissolution of enteric-coated products within a pH range from 4.5 to 7.0, and the onset of absorption can be delayed by increasing the pH resistance of the coating, without affecting the extent of absorption (see abstract). This meets the limitation of claim 1a. Additionally, the reference teaches that three different enteric-coated naproxen granulates, designed to resist solutes below pH 6.0, 6.5 and 7.0 have been developed (see p. 46, left column, 5th paragraph). This meets the limitation of claim 1a and 7-8. Since naproxen is not radiolabeled, it is non-isotopic meeting the limitation of claim 8. The reference further teaches that using an enteric coating designed to dissolve at pH 5.5, the absorption profile of granules with a diameter of about 1 mm taken with and without breakfast by six healthy volunteers in a crossover study have been measured. Blood samples were taken at appropriate times, and plasma concentrations of naproxen were assessed by high-performance liquid chromatography (see p. 45, left column, 2nd paragraph in "Enteric-Coated Naproxen Granules"). This meets the limitation of claim 1b and 3. The reference further teaches that the rate of absorption is delayed, resulting in a maximum

plasma concentration after 5-8 hours (see p. 45, left column, 3rd paragraph in "Enteric-Coated Naproxen Granules" and Figure 1). This reads on claims 2 and 10.

11. Claims 1-2, 6, 8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Hatanaka et al (Journal of Pharmacological and Toxicological Methods, 1994, 31(3): 161-165).

12. The instant claims are drawn to a method of monitoring gastric emptying in a mammal comprising a) administering a formulation comprising an agent that is formulated in a delayed-release formulation that prevents said agent from being released into the gastrointestinal tract when the pH of the gastrointestinal tract is lower than about 6.0, and b) determining the amount of time taken for an elevated concentration of said agent to be found in the blood of said mammal and the agent has been formulated into a test meal. The claims are also drawn to the agent is acetaminophen and is non-isotopic.

13. Hatanaka et al teach a method for evaluation of gastric emptying via monitoring serial serum levels of acetaminophen (APA) as an indicator, without involving animal sacrifice. Suspended test meals are administered orally to rats containing 20 mg of APA, and the animals were repeatedly bled at 15, 30, 45, 60 or 90 minutes after APAP treatment (see abstract). This reads on claims 1b, 2, 6 and 9. Since acetaminophen is not radiolabeled, it is non-isotopic meeting the limitation of claim 8. The reference further teaches that APAP is poorly absorbed from the stomach, and rapidly absorbed from the small intestine (see p. 161, right column, lines 5-6). This reads on claim 1a, since it is well known to the ordinary skilled in the art that stomach pH is around 2.0,

and the small intestine pH is around 6.0-6.5. Therefore, it is inherent that APA will not be released into the gastrointestinal tract when the pH of the gastrointestinal tract is lower than about pH 6.0. Thus, meeting the limitation of claim 1a.

Rejection-35 U.S.C. § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. Claims 1, 3-5, 7 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al (US Patent # 6562629) in view of Kolhouse et al (US Patent # 5506147) and Choe et al (European Journal of Pharmaceutical Sciences (EJPS), 2001, 14: 347-353).

17. The instant claims are drawn to a method of monitoring gastric emptying in a mammal, diagnosing a gastric emptying disorder in a mammal and gastroparesis in a

human comprising a) administering to said mammal a formulation comprising an agent that is not released into the gastrointestinal tract at a pH lower than about 6.0, and b) determining the amount of time taken, post-administration, for an elevated concentration of said agent to be found in the blood of said mammal, wherein said mammal is diagnosed as having a gastric emptying disorder if said agent is not elevated in the blood stream 120 minutes post-administration. The claims are also drawn to the said agent encapsulated in a pH-sensitive formulation and agent not present in normal dietary substances. Additionally, the claims are drawn to the total dosage of D-xylose administered in between about 5 grams and about 25 grams. Furthermore, the claims are drawn to said agent has been formulated into a test meal.

18. Lin et al (# 6562629) teach that prior art recognizes that irritable bowel syndrome is frequently associated with disordered gastro-intestinal motility (Gastroparesis) (see column 2, lines 38-42). The reference teaches a method of diagnosing or treating small intestinal bacterial overgrowth (SIBO), irritable bowel syndrome (IBS) and other disorders (see column 1, lines 18-20). It is well known in the art that if food lingers too long in the stomach, it can cause problems like bacterial overgrowth from the fermentation of food. Thus, this reads on claims 1, 10 and 11. Additionally, the reference teaches that substrates include sugars such as lactulose, xylose, lactose, or glucose. The hydrogen or methane produced in the small intestine then enters the blood stream of the host and are gradually exhaled. Typically, after an overnight fast, the patient swallows a controlled quantity of a sugar, such as lactulose, xylose, lactose, or glucose and breath samples are taken at frequent time intervals, typically every 10 to 15

minutes for a two- to four-hour period. The reference further teaches that blood was drawn from each subject, the serum was separated from the cells by a standard centrifugation protocol (see column 30, lines 63-65). This reads on claims 1b, 4-5, 9 and 10-11. Since controlled quantity of sugar is being swallowed after an overnight fast, this reads on "test meal" of claim 9. The difference between the reference and the instant claims is that the reference does not teach a delayed-release formulation that prevents agent from being released into the gastrointestinal tract when the pH of the gastrointestinal tract is lower than about 6.0.

19. However, Kolhouse et al (# 5506147) teach that the serum xylose test is one of the best non-invasive methods for diagnosing intestinal malabsorption. In this test, D-xylose, a give carbon sugar not naturally present in the body or in foodstuffs, is given orally and an estimation of the increase in serum xylose content is carried out through colorimetric determination of non-glucose reducing sugars in serum (see column 4, lines 23-29). This reads on claims 1b and 3-5. The reference further teaches methods for evaluating pancreatic insufficiency and small bowel malabsorption. The methods are useful for both human and veterinary patients such as cats, dogs, rodents, cows, horses, and other mammals (see column 6, lines 20-21 and lines 29-31). This reads on claims 10 and 11. Additionally, the reference teaches for evaluating causes of maldigestion and malabsorption in a patient comprises...a known quantity, preferably about 5 grams of xylose (see column 6, lines 32-34 and lines 39-40). This reads on claim 12. The reference further teaches that proper diagnosis is essential to avoid more

invasive and expensive procedures such as small bowel biopsy or the administration of pancreatic enzymes (see column 6, lines 25-28).

20. Choe et al (EJPS, 2001) teaches that the pellets (caffeine and acetaminophen) were enteric coated to prevent dissolution in the stomach and allow rapid dissolution in the small intestine. Previous in vitro studies demonstrated that in pH 2.0 media, drug release was not detected for 2 hours. At pH 6.0, the onset of drug release was detected within 10 minutes for the formulations with a release fraction between 0.8 and 1.0 at the 20-minute sampling time (see p. 348, right column, lines 9-15, Section 2.1). This reads on claims 1a, 7, 10 and 11.

21. Therefore, it would have been obvious to the ordinary skilled in the art to combine the Lin et al method of diagnosing or treating SIBO, IBS (Gastroparesis) or other disorders and Kolhouse et al method methods for diagnosing intestinal malabsorption, and using the enteric coated drugs for delayed release. There is a reasonable expectation of success since the it is well known to the artisans in the field that stomach pH is around 2.0 and small intestine pH is around 6.0. Choe et al teach that pellets were enteric coated to prevent dissolution in the small intestine (see p. 348, right column, lines 9-11). This further inhibits the release of the drugs in the acidic stomach pH of 2.0 and releases drugs where drugs are better absorbed (see Choe et al, p. 348, right column, lines 11-15). Kolhouse et al teach that proper diagnosis is essential to avoid more invasive and expensive procedures such as small bowel biopsy or the administration of pancreatic enzymes (see column 6, lines 25-28).

Conclusion

22. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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3/15/09
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